REMARKS

Interview

Applicants' representatives thank the Examiner for the telephonic interview, which was scheduled on August 10, 2009. Issues pertaining to §112, paragraphs 1 and 2, along with the art rejections under §102 were discussed. As per the Examiner's suggestion, original claim 1 has been recast as two independent claims, claims 1 and 4, which are directed to method(s) of detecting antigen-specific T-lymphocytes and method(s) of isolating antigen-specific T-lymphocytes, respectively. New claims, which are dependent on the aforementioned independent claims, and further directed to the elected subject matter, are presented herein. Entry thereof is respectfully requested.

Claims

Claims 1–6, 9, 10 and 13–15 are pending of which claims 10, 13 and 14 are withdrawn from consideration pursuant to the restriction requirement mailed April 15, 2008. Claims 1–6, 9 and 15 were previously examined.

Claims 7–8 and 11–12 were previously cancelled without prejudice or disclaimer.

Claims 16–26 are added by this paper.

Amendments

Claims 1 and 4 have been amended. Support for the amendment can be found, for example, in the drawings of the originally-filed application. See, Figs. 1 and 3 and the disclosure in Examples 1 and 3.

New claims 16–26 are supported, at least, by the disclosure contained in the Examples. See also, for example, the disclosure contained in paragraphs [0032], [0033], [0042], [0043], [0045], [0046], [0054]and [0055] of the published US application No. 2006-0121027.

It is respectfully submitted that the amendments do not recite new matter.

Art rejections

The rejection of claims 1–6, 9 and 15 under §102(b) as being anticipated by Assenmacher et al. (WO 99/58977) is respectfully traversed.

Assenmacher teaches that CD40L (i.e., CD154) serves as a target marker for T cells. The reference is however silent regarding the use of a CD40/CD154 system "inhibitor" for any

reason. For example, Assenmacher fails to teach or suggest that the use of CD40/CD154 system inhibitors which block or inhibit the interaction between CD40 and CD154, thereby preventing the lowering of the level of said CD154 inside or outside the T lymphocyte, allow for isolation, separation, or detection of antigen-specific T lymphocytes.

Assenmacher is also directed to other markers for T cells, e.g., CD69, which are different from the CD154 molecules of the present invention. It is further taught therein that several molecules, such as CD69, are quickly up-regulated on T lymphocytes after stimulation. Such molecules, however, are not specific enough to distinguish between antigen-specific T cells and non-antigen specific T cells. Since Assenmacher does not employ a CD40/CD154 system inhibitor having the properties claimed herein and is silent regarding the utility of CD154 in practicing the instantly claimed methods, the reference cannot anticipate the subject matter of the instant application. Withdrawal of the rejection is respectfully requested.

The Examiner's contention that Berner (*Ann Rheumatology Dis.*, 2000) further in view of Darrell (US patent application publication No. 2003/0012781) anticipates instant claims 1–6, 9 and 14 is respectfully traversed.

Berner discloses the use of CD154 as a specific prognostic or diagnostic marker in a group of patients suffering from rheumatoid arthritis. However, the reference fails to disclose or suggest a method for the detection and/or isolation of antigen-specific T cells using any method. Berner is totally silent with regard to isolating T lymphocytes that are reactive to a defined antigen or a defined mixture of antigens. Berner generically discusses the possibility of a long and increased expression of the CD154 molecule on a large number of CD4+ Th cells (average about 45% in the RA CD40Lhigh+ group in Fig.1) which, however, are not characterized by restricted antigen specificity. The authors themselves indicate that CD40L under normal conditions can be detected in a "transient" fashion on activated T cells. As such, the reference fails to teach a method for isolating or separating antigen-specific T-cells which have been activated in the presence of a CD40/CD154 system "inhibitor" which prevents degradation of CD154 molecules. Absent express or inherent disclosure in either Berner or Darrell that the use of a CD40/CD154 system inhibitor confers the ability to detect and/or isolate said antigen-specific cells based on a change in CD154 levels, the references, even at their broadest interpretation, cannot anticipate what is claimed herein. Withdrawal of the rejection is respectfully requested.

Additionally, Applicants submit that the PTO's reliance on Darrell to levy this rejection is misplaced. The Examiner alleges that based on Darrell's disclosure, Berner's anti CD40L TRAP 1 can block CD40/CD40L interactions The Examiner appears to be relying on Darrell's disclosure at paragraph [0261]of the aforementioned US publication. The assumption that the use of anti CD40L TRAP 1 antibody serves as a CD40/CD40L system inhibitor in the meaning of the invention is scientifically misplaced. Contrary to the functional properties of the CD40/CD154 system inhibitor recited in the claims, Berner's CD40L TRAP 1 antibody exhibits *agonistic activity* towards T-cell activation. See paragraph [0037] of US 2003/0012781. The agonistic effects of this antibody to the CD40L molecule result in the degradation of the CD40L receptor. Therefore the result of this action is contrary to the effects recited for the CD40/CD154 system inhibitor, as used in the present claims.

Accordingly, Berner in view of Darrell fails to anticipate the subject matter presented in claims 1–6, 9 and 14 of the instant application. Withdrawal of the rejection is respectfully requested.

The contention that Battaglia (*American Journal of Gastroenterology*, 1999) anticipates claims 1–6, 9 and 15 of the instant application is respectfully traversed.

Battaglia evaluates whether cells expressing CD40L and CD40 are detectable in the diseased specimen of ileum of patients with Crohn's disease. The results showed that several cells expressing moderate to high staining for CD40L+ were present in the affected tissue, whereas only few scattered CD40L+ cells with low intensity of staining were detected in patients with diverticulitis and in sections of histologically normal intestine resected distantly from the affected tissue of Crohn`s disease patients and of three colorectal cancers undergoing extensive surgery used as controls. The cells detected with anti-CD40L antibody are not characterized by restricted antigen specificity; only the intensity of staining was differentiated by the authors. However, as with Berner (2000), Battaglia is totally silent with regard to isolating T lymphocytes that are reactive to a defined antigen or a defined mixture of antigens. Absent express or inherent disclosure in Battaglia that the use of a CD40/CD154 system inhibitor confers the ability to detect and/or isolate said antigen-specific cells on the basis of intracellular or extracellular CD154 levels, the reference, even at its broadest interpretation, fails to anticipate what is claimed herein.

The PTO's contention that Battaglia's use of rabbit anti-sera against human CD40L would block CD40/CD40L interactions is scientifically misplaced. Firstly, absent scientific

evidence of the functional properties of such anti-sera, for example, with regard to preventing the lowering of the level of said CD154 inside or outside the T lymphocyte, the Examiner's contention has no legal basis. There is no discussion in Battaglia that the anti-sera would function in a manner recited in the claims. Accordingly, the contention that anti-sera to human CD40L comprise multiple epitopic specificities, including those that would block CD40L/CD40 interactions is simply hypothetical. Secondly, based on what is known in the art regarding antibodies against CD40L, the skilled in the art could reasonably assume that such anti-sera contain agonists. See, for example, the aforementioned Berner's reference and the agonistic activity of the TRAP1 anti-CD40L antibody disclosed therein. As is taught by Berner, such agonistic effects result in effects which are opposite to what is presently claimed, for example, degradation of the CD40L receptor. Thus, Battaglia, like Berner, also fails to anticipate or render obvious the claims of the present application. Withdrawal of the rejection is respectfully requested.

Rejections under §112

The rejection of claim 1 under this section for allegedly failing to recite clear and definitive method steps for allegedly being incomplete is respectfully traversed. The Office Action at page 5 alleges that the claim term "detecting the expression of CD154" is indefinite. At page 6 of the Office Action, a similar argument is made with respect to the rejection of claims 1–6 and 9 under §112, ¶1 (enablement). Applicants respectfully disagree with these contentions. However, purely in order to facilitate prosecution, the claims have been amended to explicitly recite the reagents employed in the detection step (e.g., antibody molecules). Applicants' amendment of the claims is not to be construed with acquiescence to this or any other ground of rejection.

The present specification provides explicit guidance on antibody-based detection assays for practicing the claimed invention in its broadest possible scope. To this end, the present specification provides a detailed description of at least two types of CD40/CD154 system inhibitors and methods for detecting CD154 levels. For example, at page 13 of the specification, a direct methodology for detection of CD154 (e.g., FACS sorting or magnetic cell sorting) is described. See also, Example 3 of the specification wherein CD154-expressing T cells are detected and isolated using FACS. In paragraph [0040], the specification provides an indirect method of detecting CD154 levels, wherein the *in vivo* effects of non-functional CD154

expression is described. As such, the PTO's contentions regarding indefiniteness are without merit.

Under items 6 and 8 of the Office Action, it is alleged that CD40 is not expressed extracellularly in vital T-cells, and as such, the claimed subject matter is indefinite and/or non-enabled. These contentions are respectfully traversed. In any event, the present claims now recite the functional properties of the CD40/CD154 system inhibitors, for example, with regard to preventing the lowering of CD154 levels either on the outside or inside the T lymphocyte. Support for this aspect is explicitly provided in Figs. 1 and 3. The claims are further directed to the detection of CD154 levels using antibodies. As such, the claims in the current form fully comply with the requirements under 35 USC §112 with respect to definiteness and enablement. Withdrawal of the rejection is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

/Sagun KC/

Sagun KC, Reg. No. L0510
For Applicant(s)

/Anthony J. Zelano/

Anthony J. Zelano, Reg. No. 27,969
Attorney for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

Attorney Docket No.: GULDE-0057

Date: August 13, 2009